Collagen Alignment Imaging and Analysis for Breast Cancer Classification

Jeremy Scott Bredfeldt

Under the supervision of [Rock Mackie and Kevin Eliceiri]

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Mortality in cancer patients is directly attributable to the ability of cancer cells to metastasize to distant sites from the primary tumor. This migration of tumor cells begins with a remodeling of the local tumor microenvironment including changes to the extracellular matrix. In breast cancer, it has been proposed that the alignment of extracellular collagen fibers surrounding tumor epithelial cells can serve as a quantitative image-based biomarker for survival of invasive ductal carcinoma patients. This dissertation reports on the design and validation of a set of optical and computational tools to enable large-scale investigations of the interaction between collagen and tumor cells.

We have built a novel imaging system which captures large field of view images of collagen and cells within tissue sections on microscope slides. The system uses second harmonic generation (SHG) imaging to capture collagen information and bright field imaging to capture information about cellular structures. We have named the system the compact automated multiphoton microscope (CAMM).

We have developed computational tools that semi-automatically score collagen interactions with tumor cells via a variety of metrics, a method we call Electronic Tumor Associated Collagen Signatures (eTACS). The eTACS system produced classifications that had statistically significant correlation with manual TACS classifications and significantly prognostic correlation with disease specific survival. The eTACS classifications accurately predicted breast cancer patient recurrence producing a disease free survival hazard ratio of 2.59. Feature rank analysis revealed that TACS positive fibers were more well aligned with each other, generally lower density, and terminated within or near groups of epithelial cells at steeper angles of interaction.

In addition, we have investigated the limitations to 3D collagen imaging with SHG and have observed that forward SHG detection is required for accurate 3D imaging. We have also developed a prototype system using single photon fluorescence optical imaging combined with physical sectioning to capture three dimensional images of whole mount tissues. We call the system SETI (Sequential Erosive Tissue Imaging). SETI is being developed to study contrast agent localization, prostate cancer progression mechanisms, and breast cancer extracellular matrix properties.